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Review

Rabbit antithymocyte globulin induction and risk of post-transplant lymphoproliferative disease in adult and pediatric solid organ transplantation: An update

Alexandre Hertig [a,*], Andreas Zuckermann [b]

[a] AP-HP, Hôpital Tenon, Urgences Néphrologiques et Transplantation Rénale, Sorbonne Universités, UPMC, Paris CEDEX 6, France
[b] Department of Cardiac Surgery, Medical University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria

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ABSTRACT

The most modifiable risk factor for post-transplant lymphoproliferative disease (PTLD) is the type and dose of induction and maintenance immunosuppressive therapy. It is challenging to identify the contribution of a single agent such as rabbit antithymocyte globulin (rATG) in the setting of multidrug therapy. Registry analyses can be helpful but are limited by methodological restrictions and inclusion of historical patient cohorts. These are typically from eras when rATG dosing was markedly higher than current dosing (e.g. total dose 14 mg/kg versus 6 mg/kg now), accompanied by higher exposure to maintenance therapies, and often an absence of antiviral prophylaxis. The largest registry analysis to assess rATG specifically found no risk of PTLD after kidney transplantation, but conflicting results have been reported, highlighting the difficulty of interpreting this type of analysis. The relative rarity of PTLD means that individually controlled trials are underpowered to assess its occurrence, but the available data do not suggest an effect of rATG. A pooled analysis of data from studies of rATG induction in kidney and heart transplantation found the incidence of PTLD to be comparable to published reports in the overall transplant population. Data on the effect of rATG dose are inconclusive, but in patients receiving antiviral prophylaxis it does not appear to be influential. Nevertheless, it would seem reasonable to employ the lowest dose of rATG compatible with effective induction, particularly in EBV-seronegative recipients and other high-risk groups such as heart–lung transplant recipients. Overall, the risk of PTLD following rATG induction therapy with modern dosing regimens and under current management conditions appears unlikely to make an important contribution to the risk:benefit balance.

Contents

Abbreviations: AHR, adjusted hazard ratio; ALG, antilymphocyte globulin; ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; aRR, adjusted relative risk; ATG, antithymocyte globulin; ATGAM, equine thymocyte globulin; ATS, antithymocyte serum; CI, confidence interval; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CTS, Collaborative Transplant Study; DSA, donor-specific antibodies; EBV, Epstein–Barr virus; HR, hazard ratio; IL-2RA, interleukin-2 receptor alpha; IRR, incidence rate ratio; ISHLT, International Society for Heart and Lung Transplantation; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; NHL, non-Hodgkin lymphoma; NK, natural killer; OPTN, Organ Procurement and Transplantation Network; PTLD, post-transplant lymphoproliferative disorder; rATG, rabbit antithymocyte globulin; RR, relative risk; SRTR, Scientific Registry for Transplant Recipients; UNOS, United Network of Organ Sharing; USRDS, United States Renal Data System.

* Corresponding author. Tel.: + 33 1 56 01 70 00.
E-mail address: alexandre.hertig@tnn.aphp.fr (A. Hertig).

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1. PTLD after solid organ transplantation

1.1. Epidemiology and risk factors

Post-transplant lymphoproliferative disorder (PTLD) remains a rare but important complication of solid organ transplantation. While it can remain a benign lymphoid hyperplasia in some cases, in others the B-cells mutate and can progress to high-grade, life-threatening lymphomas such as non-Hodgkin lymphoma (NHL). Although improved management has helped to improve outcomes [1], mortality rates remain substantially higher after the diagnosis of PTLD [2–5].

Various risk factors for PTLD have been proposed, of which recipient seronegativity for Epstein–Barr virus (EBV) with engraftment from an EBV-positive donor is the most important and well-documented, conferring more than a 20-fold increase in risk [6]. Up to 50% of PTLD cases are EBV-related [7]. The risk of developing PTLD is organ-specific, with higher rates of both PTLD [8] and NHL [9] following heart, lung and intestinal transplantation where higher doses of immunosuppression are required. An analysis of over 100,000 patients receiving a primary kidney transplant during 2000–2009 found the five-year incidence of PTLD to be 0.84% [10], compared to >1.0% in heart transplant patients [11]. Recipients of a lung or heart–lung transplant are at the highest risk due to the lymphoid-rich nature of lung tissue and importation of high levels of EBV from the donor. Age is also important: children are more likely to develop PTLD than adults [12–15] due to higher rates of seronegativity for EBV. Other possible risk factors include recent infection with cytomegalovirus (CMV) or CMV-seronegativity at time of transplant [16–18]. Clinical studies have provided robust evidence that CMV prophylaxis with virostatic agents and/or CMV immunoglobulin therapy can substantially reduce the risk of EBV-associated PTLD [19–21].

1.2. The role of immunosuppressive therapies

One of the most modifiable risk factors for PTLD is the type and dose of immunosuppressive therapy [22]. Although transplant recipients usually maintain some level of EBV-specific cytotoxic $CD8^+$ T-cells, this can vary and regimens which more intensively suppress T-cell count or function would be expected to increase the risk of PTLD. Widespread adoption of calcineurin inhibitor (CNI) therapy was associated with a significant increase in risk of NHL [23,24]. CNI agents are almost universally prescribed, at least in the immediate post-transplant period, with some evidence suggesting a higher risk for PTLD under tacrolimus versus cyclosporine [10,25]. Mycophenolate mofetil (MMF) does not appear to affect risk for PTLD [24,26]. Mammalian target of rapamycin (mTOR) inhibitors may be risk-neutral or potentially reduce risk by inhibiting growth signals in PTLD-associated EBV+ B-cell lymphomas [27]. There is evidence that mTOR inhibition blocks the replication of EBV-positive B-cells, T-cells and natural killer (NK) cells [28,29]. Treatment of rejection with high-dose steroids can adversely affect risk for PTLD [30]. For the costimulation blocker belatacept, an inhibitor of T-cell proliferation, PTLD risk appears similar to that seen under CNI therapy [31] but, of note, belatacept is contraindicated in EBV-seronegative recipients. Against this complex background, the contribution of a single element in the multidrug induction-maintenance regimen cannot be accurately identified with confidence.

Particular interest has focused on the effect of lymphocyte-depleting induction therapies. The International Society for Heart and Lung Transplantation (ISHLT) guidelines state that polyclonal induction agents may be beneficial to delay CNI introduction in patients at high risk of renal dysfunction and that antithymocyte globulin (ATG) induction may be beneficial in thoracic organ recipients at high risk for acute rejection [32], based on analyses comparing rabbit ATG (rATG, Thymoglobulin®) versus basiliximab induction [33,34]. The efficacy of rATG versus IL-2RA induction in facilitating delayed CNI therapy after kidney transplantation has also been demonstrated [35], although it is uncertain whether this strategy affects the risk of delayed graft function [36].

The ISHLT guidelines also comment that routine use of induction therapy with polyclonal preparations is indicated when complete steroid avoidance is planned. Lymphocyte-depleting agents such as muromonab -CD3 [OKT3], antithymocyte antibodies and antilymphocyte preparations can induce a profound decrease in T-cell counts. During the 1980s and early 1990s, when muromonab OKT3 and non-rATG preparations were becoming more widely used [37,38], a marked increase in the incidence of PTLD was observed [13,39]. From the late 1990s onwards, however, rATG became the most commonly used polyclonal agent in the US, with equine antithymocyte globulin (ATGAM) and OKT3 becoming virtually obsolete [37,38]. Today, rATG is the most frequently administered lymphocyte-depleting agent worldwide [40]. In addition to its effect on T-cells, rATG also exerts a wide spectrum of immunomodulatory effects, targeting B-cells, plasma cells, monocytes and dendritic cells [41].

The question of whether rATG is associated with an increased risk for PTLD after solid organ transplantation is considered here in the context of contemporary management practices.

2. Evidence from registry analyses

2.1. Interpreting registry data

The relative rarity of PTLD means that randomized trials cannot include adequate patient numbers to provide meaningful data on relative risk according to immunosuppressive regimen. Moreover, the time to onset of PTLD – a median of up to seven years post-transplant in adult kidney transplant patients [42] and three years in children [43] – means that the duration of controlled trials is often inadequate. Single-center retrospective studies can offer larger numbers, with longer follow-up, but the most substantial data are derived from analyses of transplant registry databases. Registry data, however, must be considered carefully due to a number of potential weaknesses (Table 1). Data from patients transplanted from the 1980s onwards are frequently included to provide sufficient numbers and follow-up, but must be regarded cautiously since rATG dosing was markedly higher than now [44]. Since higher rATG dosing is associated with a higher risk for PTLD [11], this is an important consideration. Transplant registries do not record rATG dosing, so it cannot be established whether analyzed cohorts received doses compatible with contemporary regimens but this seems unlikely. Opelz et al. have shown a trend to lower rates of NHL in kidney and heart transplant patients receiving ATG induction from the period 1985–1989 to 1995–2001, based on data from the Collaborative Transplant (CTS) study database [9]. While dosing information is not available, this may have been due to lower doses over time.

Table 1
Considerations for registry analyses of induction therapy and PTLD.

Long analyses periods	Requirement for large numbers and extended follow-up frequently necessitates inclusion of many years' data, during which management can evolve substantially.
Historical data	Many published registry analyses of PTLD risk only include transplants up to the early 2000s.
Selective use of rATG	rATG induction is preferentially used in patients at high immunological risk who tend to receive more intensive immunosuppression. This bias may not be fully accounted for even in multivariate analysis.
Combined analyses	Analyses often report PTLD risk for 'polyclonal antibodies' or 'ATG' instead of specifically rATG.
Mixed analysis of induction and anti-rejection therapy	Dosing for treatment of rejection tends to be higher than for induction regimens and represents an additional immunosuppressive load following induction.
Lack of dosing data	Registries typically do not record dosing but rATG dose has declined over time.
EBV status often lacking	EBV serostatus cannot be included as a covariate.
Multidrug regimens	Maintenance immunosuppression choice is not always included as a covariate.
Varying endpoints	PTLD, NHL or lymphoma

EBV, Epstein–Barr virus; NHL, non-Hodgkin lymphoma; PTLD, post-transplant lymphoproliferative disorder; rATG, rabbit antithymocyte globulin.

The risk of bias in observational registry studies is ideally addressed by multivariate analysis, but since data collection by registries is necessarily limited all relevant covariates (e.g. recipient EBV serostatus) cannot always be included. Moreover, outcomes for collective groups of induction agents (e.g. 'polyclonal induction agents' or 'ATG') cannot be regarded as applying to rATG, since there are clear differences in the risk of PTLD associated with different preparations [45,46]. It should also be noted that some studies include the use of agents either as induction therapy or as anti-rejection therapy, although those patients given anti-rejection therapy incur a substantial additional immunosuppressive load, often after receiving induction therapy. Additionally, the frequency of PTLD has declined over time, adding a further complication to analyses of transplants over a long period. Caillard et al. analyzed data from over 20,000 kidney transplants performed in France during 1998 to 2007 and found a three-fold decrease in incidence from the early years to 2006–2007 [4]. As a further complication, a comparison of PTLD data obtained via the Organ Procurement and Transplantation Network (OPTN) or via Medicare claims in the US found that the one-year incidence of PTLD after kidney transplantation was twice as high based on Medicare claims, indicating that data collection on PTLD by transplant registries is incomplete [5].

Thus, while helpful, the results of registry analyses must be examined carefully.

2.2. Registry findings: PTLD

Table 2 summarizes the registry analyses that have assessed the risk of PLTD or NHL according to use of rATG specifically or various combinations of lymphocyte-depleting agents, either for induction only or induction and anti-rejection treatment combined. Each of these analyses has the important limitation that data were included from the 1990s or even the 1980s, and often only up to the early or mid-2000s. It is reasonable to assume that rATG dosing would be higher than is typical now for the bulk of patients in these studies.

Of the three analyses that considered rates of PLTD according to whether rATG induction, specifically, was given or not [15,17,47], two found a significantly higher risk in rATG-treated patients versus patients without rATG [17,47] while one found no significant association [15]. Surprisingly, in their analysis published in 2004, Bustami et al. found the relative risk (RR) of PLTD to be significantly increased not only by rATG but also by interleukin-2 receptor alpha (IL-2RA) induction using basiliximab or daclizumab [47]. Indeed, the risk associated with IL-2RA induction was found to be higher than with OKT3 induction (RR 1.92 with daclizumab, 1.83 with basiliximab and 1.71 with OKT3). No significant difference in risk between the types of induction therapy was detected. These unexpected results are not consistent with the literature, which indicates no pro-malignancy effect of IL-2RA induction [51,54] or, indeed, a protective effect [4,5]. In a larger series ($n = 98{,}907$), Dharnidharka and colleagues found the rate of PTLD at a median follow-up of 368 days to be 0.50% (60/12,051) in patients given rATG induction [15]. In patients given no induction, the rate of PTLD was 0.56% (272/48,133), representing an adjusted relative risk (aRR) of 1.17 (95% CI 0.87, 1.58) ($p = 0.29$). The same group also assessed PTLD in the subpopulation of children ($n = 5072$). The incidence of PLTD in the 685 children given rATG was 1.90%, not significantly different to the rate of 1.44% in children given no induction (aRR 1.51, 95% CI 0.78, 2.93) [15]. In contrast, Kirk and colleagues found rATG induction to be associated with an increase risk of PTLD versus no induction in a series of kidney transplants performed during 2000 to 2004 [17] (Table 2). The incidence of PTLD in rATG-treated patients was 0.67% by day 730 (at which point data were censored), representing an RR of 1.630 ($p = 0.0025$) versus no induction.

Other registry studies of PTLD risk [5,16,48–50] have grouped multiple lymphocyte-depleting induction agents together for the purpose of analysis, in some cases including OKT3. These have shown inconsistent results (Table 2). One of these analyses considered the risk of PTLD in children undergoing heart transplantation [49]. In a cohort of 1258 children transplanted during 1993 and 2007, the risk of PTLD was assessed according to induction (Table 2). Multivariate analysis showed that the group given rATG ($n = 246$), other ATG preparations ($n = 329$), antithymocyte serum ($n = 231$) or IL-2RA ($n = 244$) induction were at a significantly reduced risk for lymphoma versus those given no induction (hazard ratio [HR] 0.45; 95% CI 0.25, 0.82; $p = 0.009$) [49]. Overall, however, since neither the specific type of induction nor the dose or duration of therapy was recorded, the findings of these studies which included groups of different induction agents are of limited value when considering rATG specifically.

Overall, registry evidence concerning the relationship between rATG and risk of PTLD is mixed, and in view of the imperfect methodology no definite conclusions can be drawn.

2.3. Registry findings: NHL

Of the analyses which examined the occurrence of NHL, rather than the wider endpoint of PLTD, only one included rATG therapy exclusively, and limited this to induction use [46]. In this study, the risk of NHL was assessed based on data from the international CTS derived from first deceased-donor kidney transplants undertaken during 1984 to 2004 [46]. rATG induction was found to increase the risk of NHL significantly compared to no induction, with a standardized incidence ratio for NHL of 21.6 for rATG-treated patients versus 9.4 for patients without induction ($p = 0.002$). However, again it is difficult to apply these findings to current practice. Approximately half the patients given rATG were transplanted during 1985–1994, and half during 1995–2004, since when rATG dosing has declined substantially [44,55,56]. Over this 20-year period there have also been very substantial reductions in exposure to maintenance immunosuppressive therapies, notably CNIs and steroids, which was not taken into account. The effect of maintenance therapy is likely to dominate over the latter part of the three-year follow-up, when PTLD incidence continued to rise. The CTS also includes a large and highly diverse group of centers from around the world, such that management practices were likely to vary widely.

Studies in which rATG was grouped with other lymphocyte-depleting agents (as induction and, in some cases, also anti-rejection therapy) have shown either a higher risk of lymphoma [24,51,52] or no effect [53], but as for PTLD it is difficult to draw relevant conclusions.

Table 2
Registry analyses of PTLD or NHL according to use of rATG or lymphocyte-depleting therapy in solid organ transplant populations.

Study	n	Registry	Time of transplant	Follow-up	Treatment group	Comparator group	Outcomes (treatment group vs comparator group)
PTLD							
Cherikh et al. [16]	38,519 (kidney)	OPTN	1997–2000	≤727 days	ATG (type not specified), ALG or ATGAM (induction or anti-rejection)	No ATG, ALG or ATGAM	No increase in PTLD RR 1.29 (95% CI 0.82, 2.03) $p = 0.27$
Bustami et al. [47]	41,686 (kidney)	SRTR	1995–2002	≤6 years	rATG (induction only)	No induction	Higher risk of PTLD RR 3.00 (95% CI 1.53, 5.89) $p = 0.001$
Dharnidharka et al. [15]	84,907 (kidney)	UNOS	1987–2003	Median 368 days (rATG group)	rATG (induction only)	No induction	No increase in PTLD ARR 1.17 (95% CI 0.87, 1.58) $p = 0.29$
Faull et al. [48]	13,516	ANZDATA	1970–2003	Not specified	T-cell depleting (induction or anti-rejection)	No T-cell depleting therapy	No increase in PTLD HR 1.2 95% CI 0.90, 1.7 $p = 0.18$
Kirk et al. [17]	59,560 (kidney)	OPTN	2000–2004	≤730 days	rATG (induction only)	No induction	Higher risk of PTLD ARR 1.630 (95% CI 1.188, 2.235) $p = 0.0025$
Kasiske et al. [5]	89,485 (kidney)	OPTN	2000–2006	≤3 years	T-cell depleting (induction only)	No induction[a]	Higher risk of PTLD HR 1.55 (1.19, 2.01) $p = 0.001$
Gajarski et al. [49]	2374 (heart)	Pediatric Heart Transplant Study	1993–2007	5 years	rATG, ATG, ATS or IL-2A (induction only)	No induction	Lower risk of PTLD HR 0.45 95% CI 0.25, 0.81 $p = 0.009$
Caillard et al. [50]	21,352 (kidney)	French PTLD registry	1998–2007	≤10 years	ATG or OKT3 (induction or rejection)	No ATG or OKT3	Borderline higher risk of PTLD AHR 1.42 (95% 1.00, 2.02) $p = 0.05$
Lymphoma							
Caillard et al. [51]	25,127 (kidney)	USRDS	1996–2000	3 years	ATG (induction or anti-rejection)	No ATG	Higher risk of NHL AHR 1.55 (95% CI 1.2, 1.99) $p = 0.001$
Caillard et al. [52]	66,159 (kidney)	USRDS	1991–2000	≤10 years	ATG (induction or anti-rejection)	No ATG	Higher risk for NHL AHR 1.37 (95% 1.17, 1.6) $p < 0.05$
Opelz et al. [46]	112,122 (kidney)	CTS	1985–2004	3 years	rATG (induction only)	No induction	Higher risk of NHL SIR 21.6 vs 9.4 $p = 0.002$
van Leeuwen et al. [24]	8,164 (kidney)	ANZDATA	1982–2003	Not specified	ATG, ALG or OKT3 (induction or rejection)	No ATG, ALG or OKT3	Higher risk of NHL IRR 2.39 (95% CI 1.08, 5.30) $p = 0.031$
Hall et al. [53]	111,857 (kidney)	SRTR	1987–2009	Median 3.5 years	ATG, ALG (induction only)	No ATG or ALG	No increase in NHL ARR 0.96 (95% CI 0.77, 1.20) $p = 0.7$

AHR, adjusted hazard ratio; ALG, antilymphocyte globulin; ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; ARR, adjusted relative risk; ATG, antithymocyte globulin; ATGAM, equine thymocyte globulin; ATS, antithymocyte serum; CI, confidence interval; CTS, Collaborative Transplant Study; HR, hazard ratio; IL-2RA, IL-2 receptor antagonist; IRR, incidence rate ratio; NHL, non-Hodgkin lymphoma; OPTN, Organ Procurement and Transplant Network; PTLD, post-transplant lymphoproliferative disorder; rATG, rabbit antithymocyte globulin; RR, relative risk; SIR, sirolimus; SRTR, Scientific Registry for Transplant Recipients; UNOS, United Network of Organ Sharing; USRDS, United States Renal Data System.

[a] Includes 10 patients receiving induction other than T-cell depleting or IL-2RA induction.

Data from registry analysis of lymphoma risk in non-renal transplants is limited. In one analysis from the CTS, Opelz et al. reported that ATG induction (including all ATG preparations) 'did not confer an added risk for lymphoma' in heart transplant recipients, but further information was not provided [9]. A prospective cohort study of all UK transplant centers has reported rates of death due to malignancy following heart transplantation according to whether patients received ATG of any type, or no ATG [57]. The population of 2086 patients was transplanted during 1995 to 2008, and thus represents a relatively recent cohort. Univariate analysis showed no effect of ATG on death from either lymphoid malignancy (1.0% versus 1.4% in non-ATG treated patients, $p = 0.38$) or non-lymphoid malignancy (3.9% versus 2.8%, $p = 0.40$); no multivariate analysis was performed.

2.4. Registry data on anti-rejection treatment

An association between rATG treatment for rejection episodes and PTLD has been less well examined. Lim et al. recently evaluated data from 7153 patients transplanted during 1997 to 2009 who received anti-rejection therapy and who were registered with the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA) [58]. Treatment for rejection with a T-cell depleting antibody (ATG, antilymphocyte globulin [ALG] or OTK3) was associated with a higher rate of malignancy of any type versus patients with no rejection (adjusted HR [AHR] 1.42; $p = 0.039$). No statistical comparison was performed versus patients with rejection treated without T-cell depleting antibody and specific types of induction agent were not compared [58].

3. Prospective studies

No prospective study of rATG in solid organ transplantation, either as induction or anti-rejection therapy, is adequately large to provide interpretable data on the risk of PTLD. As shown in Table 3, reports of PTLD are extremely rare in randomized trials. In the largest trial, by Brennan et al., 278 kidney transplant patients were randomized to a cumulative rATG dose of 7.5 mg/kg or basiliximab (40 mg in total), both with cyclosporine, MMF and steroids [61]. At one year, there were three cases of PTLD in the rATG group and none in the basiliximab group, a difference that was not significant. No other cases of PTLD have been reported in randomized trials of rATG after solid organ transplantation. Three randomized trials [59,61,63] followed patients to five years after kidney transplantation. In one of these, involving 72 patients [59], there were no cases of PTLD in the rATG cohort compared to an incidence of 8.3% in the ATGAM cohort at the end of five years' follow-up [68]. The second trial, which enrolled a larger cohort of 227 kidney transplant patients [63], reported one death from PTLD in the daclizumab group with none in the rATG arm, by five years' follow-up [69]. In the third study [61], the five-year incidence of PTLD was similar in the cohort treated with rATG (1/91, 1.2%) or basiliximab (0%; p = n.s.) [70]. No robust conclusions can be drawn other than that prospective trials do not provide data to indicate a higher rate of PTLD following rATG induction in solid organ transplant patients.

Table 3
Prospective, randomized trials reporting PTLD following rATG induction.

Study	N	Follow-up (months)	PTLD (% patients)	
Kidney transplants				
Brennan et al. [59]	72	60	rATG	0[a]
			ATGAM	0[a]
Mourad et al. [60]	105	12	rATG	0
			Basiliximab	0
Brennan et al. [61]	278	12	rATG	2.1[b,c]
			Basiliximab	0[b, c]
Abou-Ayache et al. [62]	109	12	rATG	0
			Daclizumab	0
Noël et al. [63]	227	12	rATG	0[d]
			Daclizumab	0[d]
Liver transplants				
Bogetti et al. [64]	22	3	rATG	0
			No induction	0
Boillot et al. [65]	93	60	rATG	0
			No induction	0
Heart transplants				
Mattei et al. [66]	80	6	rATG	0
			Basiliximab	0
Yamani et al. [67]	32	12	rATG 6 mg/kg	0
			rATG 1.5 mg/kg	0

ATGAM, equine thymocyte globulin; PTLD, post-transplant lymphoproliferative disorder; rATG, rabbit antithymocyte globulin.

[a] Follow-up to year 5: no PTLD in the rATG group, 8.3% PTLD in the ATGAM group [68].

[b] $p = 0.13$ versus basiliximab.

[c] Follow-up to year 5: 1.2% PTLD in the rATG group, 0% PTLD in the basiliximab group (p = n.s.) [63].

[d] Follow-up to year 5: no deaths due to PTLD in the rATG group, 1 death due to PTLD in the rATG group [69].

4. Retrospective studies

Few comparative retrospective studies have described the incidence of PTLD or NHL according to type of induction, even when antithymocyte preparations other than rATG are considered. Several of the available reports do not differentiate between types of lymphocyte-depleting induction therapy. Analyses which included patients treated with OTK3 [8,71,72], in particular, are of limited value when assessing an effect of rATG in view of the profound increase in lymphoma risk associated with OKT3 [16,46,53]. Table 4 summarizes the most relevant retrospective studies. One large analysis of 763 patients undergoing kidney transplantation during 1995 to 2001 found no cases of PTLD in any induction-treated patient, but only 213 individuals received induction and only 71 were given rATG [73]. Two other large retrospective analyses did not specifically consider rATG, but found no effect of ATG preparations in general [74,75] on the risk of PTLD. The limited available retrospective data from liver [78] and lung [76] patients also show no effect of rATG therapy on risk of PTLD. In small bowel transplantation, one series has reported an increased rate of PTLD in a series of children given rATG induction at a cumulative dose of 7.5 mg/kg [77]. rATG in this study was given to the 16 patients who had high titers of de novo donor-specific antibodies (DSA) ($n = 11$) or to treat rejection ($n = 5$). All other patients were given the IL-2 receptor antagonist basiliximab. During follow-up ranging from one to nine years, six of the rATG-treated patients (37.5%) developed PTLD. However, each of these patients also received sirolimus with standard-exposure CNI, a combination which has been associated with an unacceptably high rate of PTLD in children undergoing kidney transplantation and, indeed, led to premature discontinuation of one study due to PLTD risk [79]. It seems likely that these children undergoing small bowel transplant were over-immunosuppressed, contributing to the high rate of PTLD [77].

One retrospective study has described the occurrence of PTLD in a series of 54 patients undergoing a second kidney transplant during 2004–2010 who received a second course of rATG induction, comparing this to a matched cohort of patients receiving rATG for the first time, after a primary kidney transplant [80]. The median total rATG dose was 9 mg/kg in the retransplanted patients and 7 mg/kg in the primary transplants. Only one case of PTLD was observed, in a control patient.

5. Pooled data

Marks and colleagues performed a systematic review to identify published reports of PTLD in adult solid transplant recipients given rATG induction [11]. Eleven studies were in kidney transplantation (1392 patients in total) and five in heart transplantation (854 patients). Seven were prospective studies, and four were retrospective analyses. The median follow-up time was five years (range 3 to 10 years). The observed rate of PTLD was 0.98% overall and 0.93% in kidney transplant

Table 4
Retrospective comparative analyses of PTLD risk according to induction therapy.

Study	n	Time of transplant	Follow-up	Induction group	Comparator group/s	PTLD
Kidney transplantation						
Castro et al. [73]	763	1995–2001	≥1 year	rATG (n = 71)	IL-2RA (n = 66), OKT3 (n = 44) or no induction (n = 550)	rATG 0%, IL-2RA 0%, OKT3 0%, no induction 0.4%
Hardinger et al. [68]	72	1996–1997	5 years	rATG (n = 48)	ATGAM (n = 24)	rATG 0%, ATGAM 8.3% (n.s.)[a]
Bichari et al. [74]	1265	1979–2006	10 years	ATG (type not specified) (n = 323)	IL-2RA induction (n = 300), OTK3 (n = 21) or no induction (n = 621)	2.5% overall Multivariate analysis showed no difference in risk between ATG, induction or no induction (data not provided)
Kaden et al. [75]	760	1987–1998	5.5–17 years	ATG-Fresenius (single 9 mg/kg dose) (n = 522)	No induction (n = 238)	0.4% in both groups (p = 0.940)
Lung transplantation						
Shyu et al. [76]	336	1998–2005	5 years	rATG (n = 43)	Alemtuzumb (n = 127), daclizumab (n = 73) or no induction (n = 93)	rATG 3%, alemtuzumab 4%, daclizumab 3%, no induction 6% (p = 0.864)
Small bowel transplantation						
Nassif et al. [77]	81 (children)	2003–2012	1–9 years	rATG (n = 16)	No ATG (IL-2RA in the majority of cases) (n = 59)	rATG 37.5%, no rATG 5.1%[b]

ATGAM, equine thymocyte globulin; ATG-Fresenius, anti-human T-lymphocyte immunoglobulin from rabbits immunized with Jurkat cells; ATGAM, equine thymocyte globulin; IL-2RA, interleukin 2 receptor alpha; n.s., not significant; PTLD, post-transplant lymphoproliferative disorder; rATG, rabbit antithymocyte globulin; tx, transplantation.

[a] Significantly lower rate of malignancy with rATG versus ATGAM (6% vs 21% p = 0.01).

[b] All six rATG-treated patients who developed PTLD received sirolimus in combination with standard-exposure tacrolimus; two of the patients additionally received rATG to treat rejection.

patients, broadly comparable to published reports in the transplant population overall [10]. The studies included in the analysis did not, however, permit comparisons with no induction or other types of induction agent since few were designed to compare rATG therapy with other regimens.

Two Cochrane database analyses have included information on the risk of PTLD after liver [71] or lung [81] transplantation. In both analyses, no difference in the rate of PTLD was found between patients given any type of T-cell antibody induction (including rATG, ATGAM or ALG) versus no induction [71,81], but the robustness of the data were limited by a relative paucity of studies.

6. rATG and EBV infection

Given the well-established association between EBV infection and risk of PTLD [6], it is interesting to note the findings of a retrospective review undertaken in 197 pediatric liver transplant patients by Lu et al. [78]. The incidence of EBV viremia at one year post-transplant was not significantly different in patients treated with rATG (73%) or daclizumab (63%) and multivariate analysis found no effect of either type of induction versus no induction on the risk of viremia. In one cohort of 383 adult patients undergoing consecutive kidney transplants during 2002 to 2010, the relatively high ATG-Fresenius dose of 21 mg/kg was associated with an increased risk of EBV infection ($p < 0.001$) [82]. Since lowering immunosuppressive load is usually effective in reducing the EBV viral load, this may have been an effect of over-immunosuppression. Interestingly, in the US registry analysis described by Kirk et al., a subpopulation analysis was undertaken in EBV-seronegative children, who are known to be at high risk for PTLD [17]. The relative risk of PTLD was found to be particularly high in the EBV-seronegative children given rATG (8.56), a group that appears vulnerable to over-immunosuppression.

An intriguing question is whether there is an interaction between antiviral prophylaxis after transplantation and risk of PTLD under rATG therapy. While prophylactic virostatic agents are primarily given to prevent CMV infection, they can also suppress EBV infection [83,84] and lower the rate of EBV-associated PTLD [19,20,85,86]. On first sight, these data are intriguing. Acyclovir, ganciclovir and valganciclovir are pro-drugs that require phosphorylation to become active. Phosphorylation occurs by the action of viral thymidine kinases which are supposedly inactive in EBV-infected B-cells during the latency program of the virus. However, these thymidine kinases are active during the lytic phase, and by reducing the dissemination of the virus, they may reduce the pool of EBV-infected B-cells, the source of PTLD. This could explain why acyclovir and ganciclovir have been found to exert a dramatic preventative effect on early PTLD in kidney recipients [85].

In the pooled analysis undertaken by Marks et al. described above [11], the rate of PTLD in kidney or heart transplant patients given antiviral prophylaxis was less than half that observed in patients without any antiviral prophylaxis (0.63% versus 1.61%) [11]. Interestingly, in the group who received antiviral prophylaxis (n = 1438), the rate of PTLD was low regardless of whether rATG dose was <7.5 mg/kg (0.72%) or ≥7.5 mg/kg (0.30). The greatest influence on PTLD risk was absence of antiviral prophylaxis, not use of induction therapy. These data merit further exploration.

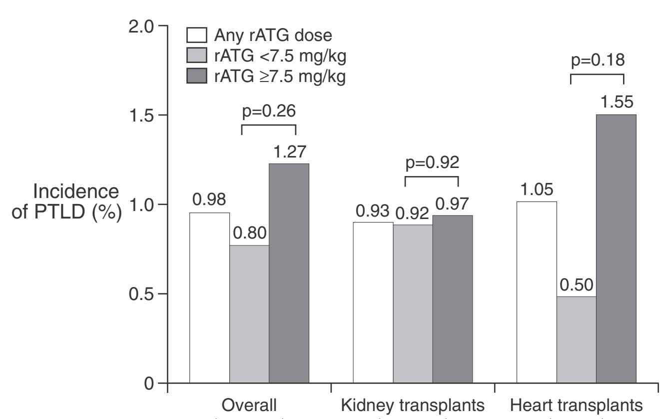

Fig. 1. Pooled analysis of incidence of PTLD in patients receiving rATG after kidney transplantation (11 studies) or heart transplantation (5 studies) according to cumulative rATG dose [11]. PTLD, post-transplant lymphoproliferative disease; rATG, rabbit antithymocyte globulin.

7. Effect of rATG dose

The pooled analysis of clinical trials by Marks et al. included an evaluation of the rate of PTLD according to the cumulative dose of rATG (Fig. 1) [11]. Given that the conventional induction regimen for rATG has been 1.5 mg/kg for five days, the authors used a cut-off point of 7.5 mg/kg. Overall, patients receiving less than this dose had a lower observed rate of PTLD (0.80% versus 1.27% in those given 7.5 mg/kg or more), but this difference was largely confined to heart transplant recipients (Fig. 1) and all differences were non-significant. Contemporary regimens now typically apply a total rATG dose of 6 mg/kg [44,55], below the cut-off used by Marks and colleagues.

One large single-center report, published only in abstract form to date, has described 30 years' experience in 4809 kidney transplant patients, 1798 of whom received rATG [87]. Over the analysis period, the initial dose of rATG remained unchanged at 7.5 mg/day, but the duration of administration steadily declined to less than 10 mg/kg. Maintenance immunosuppression also evolved over the same period, but it was noted that the incidence of PTLD fell from 4% to 1% over the most recent 10 years.

Other data relating to rATG dose have generally been provided from studies in children. One prospective assessment of 72 pediatric heart transplant recipients found that patients who developed PTLD had received a higher number of ATG doses than patients without PTLD (mean 4.3 versus 2.7, $p = 0.03$) [21]. However, it is difficult to draw conclusions since induction therapy comprised only two doses. Subsequent doses were given to treat rejection i.e. those patients receiving higher doses had experienced rejection. Moreover, several different ATG preparations were given i.e. rATG, ATGAM, and ATG-Fresenius (ATG-Fresenius is an anti-human T-lymphocyte immunoglobulin from rabbits immunized with Jurkat cells). An early analysis from the same center prospectively assessed EBV load and risk of PTLD in 41 children undergoing heart transplantation, but only 20% received rATG (67% received horse ATGAM) [88]. With this caveat, it is still of interest to note that the mean number of doses of ATG (of any type) was higher in patients who developed PTLD versus no PTLD (mean 4.2 versus 1.8 doses; $p = 0.03$). There are, however, reports of low rates of lymphoma in pediatric recipients of a heart transplant despite high doses of rATG: for example, Di Filipppo et al. found only one case of PTLD during 10 years' follow-up in 33 patients given up to 8 mg/kg of rATG [89].

8. Conclusions

Accurate assessment of the risk of PTLD in solid organ transplant patients under rATG induction is challenging. The benefits of high patient numbers and long duration of follow-up provided by registry analyses are offset by older datasets, by inclusion of multiple induction agents with no differentiation between polyclonal preparations, doses or duration of therapy, and by the risk of incomplete adjustment for selection bias. A major bias is the burden of immunosuppression during the maintenance phase of the graft. In renal transplantation, most centers preferentially use rATG, as opposed to non-depleting agents, for patients at high immunological risk. These patients typically also receive higher doses of CNI and steroids over the long term, and have a higher incidence of acute rejection episodes which, in turn, require additional anti-rejection therapies. Because PTLD is a viral disease, facilitated by a decrease in cellular immunity, any study which aims to isolate the role of a specific agent in the development of PTLD should adjust for the cumulative effect of all other immunosuppressive drugs administrated in the recipient before the onset of PTLD, which is never the case in registry analyses.

Randomized trials cannot provide meaningful data on the risk of PTLD associated with rATG administration due to their small size and short duration. Retrospective studies, often involving relatively high numbers of patients, do not indicate any increased risk for PTLD with rATG but are inherently less reliable than prospective controlled trials. In general, concerns about an increased risk of PTLD with rATG induction after solid organ transplantation stem largely from registry studies with poor methodology and which do not take account of dosing or length of treatment. These have analyzed patient cohorts transplanted when rATG doses were higher than today and when management practices were different, such as lower use of antiviral prophylaxis.

While the available data give no clear guidance, it would seem reasonable to employ the lowest dose of rATG compatible with effective induction. Recent reviews concluded that a cumulative dose of 6 mg/kg is generally appropriate for use as induction therapy after solid organ transplantation [44,56]. Although data are limited to one pooled analysis, it is possible that patients receiving antiviral prophylaxis are less vulnerable to an effect of high rATG doses. Careful use of rATG may be warranted in EBV-seronegative recipients who do not receive antiviral therapy, particularly in children and other high-risk groups such as heart–lung transplant recipients. In children, it has been suggested that a maximum cumulative rATG dose of 3–4.5 mg/kg may be appropriate [56].

In conclusion, modern immunosuppressive regimens employ rATG induction at doses which are markedly lower than in the past, and minimize maintenance dosing regimens with modification of both induction and maintenance therapy in at-risk patients. In such circumstances, the risk of PTLD does not appear to be an important contributor to the risk benefit balance associated with rATG induction.

Conflicts of interest

Alexandre Hertig has received grants or research support from Novartis and Astellas, has acted as a consultant to Novartis and BMS, has received speaker's honoraria from Sanofi, and has received honoraria for membership of advisory boards from Novartis and Sanofi. Andreas Zuckermann has received research funding and is a member of an advisory board for Sanofi-Genzyme.

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